IN THE UNITED STATES BANKRUPTCY COURT
FOR THE DISTRICT OF DELAWARE

In re:	)	Chapter 11
	)	
W.R. Grace & Co., et al.,	)	Case No. 01-01139 (JKF)
	)	(Jointly Administered)
Debtors.	)	
	)	

CLAIMANTS REPRESENTED BY THE LAW FIRM OF MOTLEY RICE LLC'S SUBMISSION AND ADOPTION OF EXPERT REPORTS REGARDING THE ADJUDICATION OF LACK OF HAZARD ISSUES, AS DESCRIBED IN THE 15TH OMNIBUS OBJECTIONS

In accordance with the Court's Amended Order Setting Various Deadlines Regarding Objections to Asbestos Property Damage Claims, dated October 13, 2006, the Claimants[1] represented by the law firm of Motley Rice LLC (hereinafter the "Motley Rice" Claimants) hereby submit their Submission and Adoption of Expert Reports. Plaintiffs hereby submit the expert reports of Drs. Richard A. Lemen, Samuel P. Hammar and Arnold R. Brody and adopt expert reports previously admitted in this litigation for the Adjudication of Lack of Hazard Issues, as Described in the 15th Omnibus Objections.

I.

On December 7, 2006, the Motley Rice Claimants filed their Preliminary Designation of Fact and Expert Witnesses Regarding Adjudication of Lack of Hazard Issue as Described in the 15th Omnibus Objections. In this pleading, the Motley Rice Claimants identified their lack of hazard expert and fact witnesses and the subject matter

[1] The Asbestos Property Damage Claimants represented by the law firm of Motley Rice LLC, on whose behalf this Expert Report Submission is served, include the following: American Legion (Claimant #3406); Catholic Diocese of Little Rock (Claimant #3515); CHP Associates (Claimant #2977); Fargo Housing Authority (Claimant #3405); Port of Seattle (Claimants #9645, 9646 and 9647); and State of Washington (Claimants #6937, 6938, 6939, 6940, 6941, 6942, 6943 and 6944).

of their testimony. The Motley Rice Claimants hereby fully incorporate by reference all matters set forth in said designation.

II.

On December 21, 2006, the Motley Rice Claimants filed their Submission of Expert Reports, and Identification of Any Additional Fact Witnesses and General Subject Matter Testimony Regarding the Schedule for the Adjudication of Product Identification Issues, as Described in the 15th Omnibus Objections. In this pleading the Motley Rice Claimants submitted their expert reports and/or other documentation regarding the issue of product identification. The Motley Rice Claimants hereby fully incorporate by reference all matters set forth herein.

III

Pursuant to this Court's Order and Rule 26 of the Federal Rules of Civil Procedure, the Motley Rice Claimants hereby file this Submission of Expert Reports of Drs. Richard A. Lemen, Samuel P. Hammar and Arnold R. Brody, attached hereto as Exhibits A, B and C.

IV.

The Motley Rice Claimants reserve the right to supplement this Submission and hereby adopt additional expert reports and/or documentation filed in this litigation. The Motley Rice Claimants further reserve the right to call any other expert or fact witnesses designated by any other party involved in this matter. Specifically, Motley Rice Claimants reserve the right to:

1. Adopt as an expert or fact witness any other such witness listed by any other party, including Claimants, the Debtor, or the PD Committee regarding lack of hazards;
2. To call as an expert of fact witness any such witness listed by any other party, including Claimants, the Debtor, or the PD Committee. The subject of such testimony will be the same as that listed by the other party;
3. Incorporate herein all W.R. Grace fact or expert witnesses, and their depositions for purposes related to the trial on lack of hazards;
4. Utilize W.R. Grace depositions to authenticate any documents attached to Claimants filings for identification of W.R. Grace products or documents relative to W.R. Grace objections based on lack of hazards;
5. Identify additional fact and expert witnesses regarding W.R. Grace products, and the known hazards of such products.

Dated: January 16, 2007

Respectfully Submitted by:

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EXHIBIT A

DR. RICHARD LEMEN – JANUARY 2007 REPORT

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Report of Dr. Richard A. Lemen

This report is intended to express my opinions on asbestos related diseases, based on the existing scientific data base, including the epidemiology of asbestos-related diseases; the ability of asbestos-containing materials within buildings to increase the risk of asbestos-related disease; the hazardous nature of asbestos-containing products and the ability of such products to cause disease in humans; the nature of asbestos fiber types and their ability to cause disease; the fact asbestos fibers can cause disease when released from products contained asbestos, including chrysotile and tremolite containing materials; the ability of asbestos fibers to affect persons not directly working with the asbestos-containing products; the synergist effect of combining asbestos exposures with cigarette smoking; and the various methods to control exposures to asbestos and their effectiveness, including TLV, guidance limits and regulations for asbestos. The findings of this report are made based on my training and experience in studying asbestos for the last 35 years. My qualifications and experience are described in my attached CV.

Asbestos-Related Diseases

Asbestosis

Asbestosis is a chronic lung disease due to the inhalation of asbestos fibers, either of the amphibole or serpentine type, and is characterized by diffuse interstitial fibrosis and frequently is associated with pleural fibrosis or pleural calcification. X-ray changes are usually small irregular opacities occurring mainly in the lower and middle lung fields. The pulmonary fibrotic changes develop slowly over the years---often progressively, even without further exposures---and their radiographic

detection is a direct correlate of their extent and profusion. In some cases, minor fibrosis with considerable respiratory impairment and disability can be present. Pulmonary hypertension is frequently associated with advanced asbestosis and the resultant cor-pulmonale (right-sided heart failure) may be a cause of death. In some asbestos-exposed cohorts this has accounted for 12 to 20% of the deaths (Kleinfeld et al, 1967; Krige, 1966). Asbestosis is a progressive disease even in the absence of further exposure (OSHA, 1986). Individuals diagnosed with pulmonary asbestosis are at a higher probability of developing and dying of cancer (HMSO, 1949; Buchanan, 1965; O'Donnell, et al, 1966; Lewinsohn, 1974; Berry, 1981). Nine member clinics, from the Association of Occupational and Environmental Clinics (AOEC), reported seeing 2057 patients between 1997 and 2000 for asbestos-related conditions, 95% of whom were diagnosed with asbestosis/parenchymal disease principally in the construction (SOC code 63-64); production working occupations i.e. welders, labors, machine operators etc. (SOC 71, 73-78) and the handlers, cleaners, helpers & laborers (SOC 86-87) occupational categories (Hunting & Gavitt, 2003). Most researchers believe that asbestosis is linearly related to cumulative exposure and because very low concentrations of asbestos do not result in radiological, pathological or clinical evidence of lung fibrosis suggests there may well be a threshold for asbestosis (Karjalainen, 2002).

Pleural Disease

Siegal et al., (1943) reported of pleural plaques, in talc workers exposed to talc dusts containing tremolite asbestos. Siegal et al. also noted after their paper was written that it was reported in the Fifty-Seventh Annual Medical Report of the Trudeau Sanatorium that experimental production of intrapleural adhesions in animals were reported. In the 1950's other reports of pleural calcification and pleural activity were reported in asbestos workers: Smith (1952) tremolite talc; (Jacob & Bohlig, 1955) pleural thickening among a cohort of 343 cases in Dresden Germany; Fehre (1956) observed pleural calcifications thought to be due to inhalation of silica, however, the author concludes they are similar to those observed in persons exposed to asbestos dust; and Frost et al. (1956) observed 22 cases of x-ray changes in 31 laggers surveyed from a trade union in Denmark with 19 having had pleural abnormalities including pleural thickening and calcifications. In a review of 6 studies on the complication of pleural plaques in asbestosis patients, in China, found a range for plaques of from 34.2% to 100% and in an another 6 studies of asbestos workers the prevalence of pleural plaques ranged from 1.3% to 29.8% (Cai et al., 2001).

Calcifications resulting from fibrous dust are usual bilateral, and situated on the parietal pleura and probably very small amounts of dust are capable of causing pleural calcifications which appear to be due to mechanical irritation (Kilviluoto, 1960). The plaques are progressive and sometimes do cause adverse respiratory symptoms, such as dyspnea (breathlessness) and decrements in pulmonary function while it is more likely that diffuse pleural thickening will cause functional impairment (McMillan and Rossiter, 1982; Sheers, 1979; Rosenstock and Hudson, 1986; Rosenstock et al., 1988). The Disease pleural thickening is considered a marker of past exposures by some (Hillerdal, 1980). There is evidence that persons with pleural plaques are more likely to develop asbestos-induced parenchymal fibrosis than those without such plaques (Rosenstock, 1994). Further is has been found that, in occupationally exposed persons, that appreciable amounts of fibers were found in their thoracic lymph nodes as well as in pleural plaques (Dodson et al., 1991a & 1991b). In some situations, asbestos-induced pleural plaques are the most common finding of the asbestos-related abnormalities (Karjalainen, 2002). Asbestos and erionite fibers appear to be the only causative agents for the typical pleural plaques with a usual latency of several decades. Others believe that there is evidence that individuals with asbestos-induced pleural plaques are at a marked increased risk of developing and dying of lung cancer or malignant mesothelioma.

Fletcher (1972) reported asbestos-exposed shipyard workers diagnosed with pleural plaques were at a 137 percent greater risk from dying of cancer of the lung (16 obs. vs. 6.74 exp.; $p < 0.005$; calculated RR = 2.37, 95% CI: 1.36 - 3.86), none of which had radiological evidence of asbestosis; a 2900 percent increased risk of dying from mesothelioma (3 obs. vs. 0.10 exp.; $p < 0.001$; calculated RR = 30, 95% CI: 6.19 - 87.67) and a 55 percent increase risk of other cancers when compared to the general population of the same age but not occupational exposed to asbestos. The workers included a variety of crafts workers. In another study of shipyard workers, Edge (1976) reported that workers with mixed asbestos exposures and pleural plaques (without evidence of pulmonary fibrosis) had a 2.5 times greater risk of developing carcinoma of the bronchus, when compared to the matched controls who had a 1.2 times greater risk without plaques probably reflecting a greater dose. Also, Edge observed 3 mesotheliomas in those with plaques while none occurred in those with no plaques. Edge (1979) in a later study of shipyard workers found that out of 156 workers with asbestos-induced pleural plaques, but with no other radiographic evidence of pulmonary fibrosis, had 8 deaths from lung cancer compared to 3 in those without pleural plaques, a 2-fold increase and 13 mesotheliomas among those with plaques and 2 in those without plaques, a 6-fold increase. Smoking could not explain the increase in lung cancer in these workers. Edge also observed that if he removed the one mesothelioma occurring within

the first 2 years of observation that 7 cases occurred in 2637 man-years of observation for an incidence of 1/377 cases per year.

Hillerdal noted several factors related to pleural plaques: first, plaques are always more widespread on autopsy than x-ray; two, in populations without endemic plaques 80-90% of the strictly defined plaques are due to occupational exposures and they can also be found in persons with low-level exposures; third, asbestos bodies are more prevalent in persons with pleural plaques; fourth, pleural plaques are related to time after exposure to asbestos than to the dose; fifth, in industrially developed countries 2-4% of all males over the age of 40 usually have plaques; sixth, plaques themselves are usually harmless, but as an indicator of exposure they are indicators of sufficient latency for asbestos-induced cancers, e.g. persons with pleural plaques are twice as likely to develop lung cancer as those without such plaques and those with plaques are at greater risk of mesothelioma; seventh, those with pleural plaques, in general, have lower lung function; and finally, persons having high rates of pleural plaques from living in areas of local deposits of asbestos such as tremolite, amosite and crocidolite have a high risk of mesothelioma while those with high rates living in areas of anthophyllite do not (Hillerdal, 2001). In residents of Da-yao, China with environmental exposure to crocidolite pleural plaques were prevalent in 11% of those over 20 years of age and in 20% in those over 40 years old (Luo et al., 2003).

Pleural effusions, diffuse pleural thickening and rounded atelectasis are also caused by exposure to asbestos (Tossavinen et al., 1997).

Lung Cancer

In early studies asbestosis was frequently found in conjunction with lung cancer among workers exposed to asbestos (Merewether, 1949; Doll, 1955; Buchanan, 1965). This led some to speculate that asbestosis was necessary and somehow associated in the etiology of lung cancer among those exposed to asbestos, some attributing this association to the "scar" theory of carcinogenesis. This is not strongly supported for all asbestos-associated lung cancers according to Hillerdal (1994), since he observed that a majority of tumors were squamous cell cancers and not adenocarcinomas. Adenocarcinomas were found most commonly among patients with asbestosis and in the lower lobes of the lung, where asbestosis is most prevalent. It is true, however, in some cases of advanced asbestosis, that scar carcinomas may develop as an outgrowth of uncontrolled fibrogenesis, just like they do with usual interstitial pneumonitis (UIP), the typical pathologic lesion in asbestosis (Cullen, 1987). Asbestos exposure appears to increase the risk for all histological

types of lung cancer (Karjalainen, 1994). Both those with asbestos exposure and also those with asbestosis have risks of lung cancer higher than found in the general population not exposed to asbestos (Broderick et al., 1992). It is more likely that asbestosis is not a precursor to lung cancer, but that both are independent diseases related with a dose-response from exposure to asbestos, and that cancer of the lung can and does occur in the absence of asbestosis (Roggli et al., 1994; Abraham, 1994; Karjalainen, 1994; Hillerdal, 1994; and Jones et al., 1996). McDonald et al. (1994) have presented epidemiological data showing increased risk of lung cancer in occupations with exposure to asbestos in the absence of radiological evidence of pulmonary fibrosis. Hillerdal (1994), in a well designed study having sufficient statistical power, found lung cancer to occur in patients with bilateral pariental pleural plaques but without radiological evidence of asbestosis. Lung cancer continues to be statistically elevated among asbestos workers under surveillance [SIR 1.14; 95% CI 1.01-1.26] (Koskinen et al. 2003). In a Chinese study of 8 asbestos factory cohorts and 3 mining cohorts that the complication rate of lung cancer among asbestotics ranged from 3.5% to 26.9% (Cai et al., 2001). That exposure levels for carcinogens are safe (including asbestos) is brought into question by the findings that the lungs may accumulate massively more cancer-causing airborne particles than previously thought. The bifurcations within the lung may allow high concentrations of particles to build up as much as 100 times as in the other parts of the lung (Balashazy et al., 2003).

Smoking and Risk of lung cancer increases more than just additive but are multiplicative nature. Both asbestos and smoking are independently capable of increasing the risk of lung cancer. One of the largest cohorts of asbestos workers to demonstrate this is that of the North American insulators studied by Dr. Selikoff. His co-investigator Dr. E. Cuyler Hammond of the American Cancer Society (ACS) reported among 12,051 insulation workers with more than 20 years of work experience when compared to a control population from the ACS of 73,763 men both of whose smoking history was known that the RR went up to 53.24 for smoking asbestos insulation workers compared to non-smoking asbestos workers with 5.17 and non-asbestos insulation workers, as controls, of 10.85 (Hammond et al., 1979). In addition, another summary of smoking and asbestos exposure combined, reported the RR for 3 additional studies to be 8.2; 32.7; and 25.7 (Blennerhassett et al., 1995). Asbestosis patients had an Standard Mortality Ratio (SMR) of 15.47 (95% CI: 11.2-20.8) for lung cancer (Morinaga et al., 1993). An analysis of 23 studies on asbestos exposure and smoking shows that asbestos multiplies the risk of lung cancer in non-smokers and smokers by a similar factor and that the combined relationship of exposure to asbestos and smoking can be best described by a multiplicative rather than an additive model (Lee, 2001).

The relative risk for lung cancer has varied from 1.0 (Knox et al., 1968) to 17.6 (Elmes and Simpson, 1971) with an average 9.8 relative risk. The prognosis and treatment of asbestos induced lung cancer is no different than lung cancer having another etiology. It appears that all cell types of lung cancer can occur in asbestos workers and that the presence or absence of one cell type cannot be used to prove or disprove and association of asbestos exposure with the lung cancer (Churg, 1985). Since 1997 asbestos has been the leading cause of lung cancer in Japan (Morinaga et al., 2001). Most studies of asbestos workers have been among white males, however, when race is considered black men also are at a higher risk when exposed to asbestos. One study reports an OR of 1.8 (95% CI: 1.03-3.1) for lung cancer in black men, however, when using SEER data from 1988-1992 mesothelioma was higher in white men than black (1.7 vs 0.9/100,000) (Muscat et al., 1998). In a survey of Hungarian workers exposed to asbestos with lung tumors 72 patients (24%) of 297 had cumulative occupational asbestos exposures assessed as below 25 fibre-years (between 0.01 and 23.9 fibre-years) (Mándi et al., 2000). In West Germany, a case-control study reported that the results supported a doubling of the lung cancer risk with 25 fiber-years of exposure and when using a two-phase logistic regression model showed OR increases from 0 to ≤1 fiber-years (0.86; 95% CI: 0.55-1.33; 1 to ≤10 fiber-years (1.33; 95% CI: 0.80-2.33); and 10+ fiber-years (1.94; 95% CI: 1.10-3.43) which are similar to those found by Stayner et al., (1997) and Dement & Brown (1993) (Pohlabeln et al., 2002). A case-referent study of Swedish lung cancer patients found clear evidence for the risk of lung cancer at low-dose levels and that the use of linear extrapolation from high exposure levels may underestimate the risks at low doses. For those exposed at 1-2.49 fiber-years the relative risk (RR) was 2.7 (95% CI: 0.7-9.5) in never smokers and for those smoking >20 cigarettes/day the RR was 80.6 (95% CI: 20.2-322.0) (Gustavsson et al., 2002). There is also evidence of an increased number of multiple primary cancers at the same time among those exposed to asbestos compared with the general population (Selikoff et al., 1979).

Mesothelioma

Mesothelioma is a cancer of the mesothelium, the thin lining that covers the major internal organs of the body. The rarity and the fact that this type tumor is strongly associated with exposure to asbestos make it a "signal tumor". This means that it is considered an epidemiological marker for exposure to asbestos (Roglli et al., 1992 & Mullen et al., 1991). Wagner was the first to recognize and report primary pleural tumors in 1870 (Wagner, 1870). Credit is given to Adami for the term

mesothelioma in 1909 (Adami, 1908). The modern concepts concerning the pathology and diagnosis of mesothelioma were set forth in 1931 by Kemperer and Rabin (Klemperer & Rabin, 1931). Gloyne described the migration of fibers to the lymph stream and especially into the mediastinal glands in a person with asbestosis (Gloyne, 1933). It is interesting to note that Hesychius the lexicographer defined asbestosis as stuccoing or plastering and Cooke gave the name asbestosis which now, in addition to asbestosis, "may indeed stucco the pleura or the peritoneum" as well as other organs having mesothieal linings (Hill, 1966). The dose-response relationship for mesothelioma was first shown among textile workers exposed to asbestos and then among gas masks workers, miners and millers and shipyard yard workers (Newhouse & Berry, 1976; Jones et al., 1979; Hobbs et al., 1979; & Sheers & Coles, 1980).

This uncommon tumor, mesothelioma, is now today being reported in almost every major study of persons exposed to asbestos. Some have estimated that pleural mesothelioma occurs with an incidence of 1 for every 2 lung cancers; however, these estimates have generally be related to the overall mortality within specific cohorts of asbestos workers and in some based on cumulative asbestos exposure of 25 or more fiber-years and can be rather misleading either as overestimates or *vis versa* (Mandi et al., 2000). In one analysis the authors have thrown out the three highest and the three lowest ratios and report then a range of ratios for mesothelioma to lung cancer from 1.0 to 5.2, however, they actually threw out the 4 lowest so the range is really 0.5 to 5.2 (median 2.4). If they had looked at the entire range it would have a range from 0.3 to 18.5 (median 3.67) (McDonald & McDonald, 1981). Thus, the actual ratio does vary between studies and any reflection on just the median ratio is misleading. Pleural mesothelioma incidence has been increasing in all asbestos using countries despite control measures put in place since the 1970s (Hemminki & Li, 2003). Peritoneal mesothelioma is a much rarer tumor than pleural, for example in Sweden the male incidence is 10-fold less than for pleural tumors, but in females it is somewhat higher or about ½ that of the pleural tumor. Swedish males have shown no increase in peritoneal mesothelioma since 1985 but in females peritoneal mesothelioma has been steadily increasing and has surpassed the rate of pleural mesothelioma (0.16/100,000) (Hemminki & Li, 2003a). The National Institute for Occupational Safety and Health in conjunction with The National Center for Health Statistics reports between 1987-1996 that various work groups had extremely elevated PMR's for pleural malignancies such as insulation workers at 23.08 (95% CI 1059-43.80); boilermakes at 15.37 (95% CI 7.68-27.50); plasterers 11.61 (95% CI 3.76-27.13); sheetmetal workers 10.35 (95% CI 6.55-15.54); plumbers, pipefitters and steamfitters 7.02 (95% CI 5.12-9.40) as well as 13 other specific occupations with PMR's of 2 or greater. They

also report these occupations taking place in several industries including ship and boat building and repairing with a PMR for pleural tumors of 12.60 (95% CI 8.75-17.52) and petroleum refining with a PMR of 5.76 (95% CI 3.29-9.35). Another 15 industries also had PMR's over 2 with all 95% Confidence Intervals that did not include 1 (NIOSH, 1999). The finding of such a high PMR for ship and boat building and repair is consistent with the study of Tagnon et al. of the shipbuilding in coastal Virginia which found 61 cases of mesothelioma among white males with a relative risk of 15.7 for the shipyard employees reporting exposure to asbestos compared to 4.9 for shipyard employees who did not report exposure to asbestos (Tagnon et al., 1980).

The ratio of occurrence for mesothelioma in the pleural area to the peritoneal area appears to be associated with the degree of exposure (Newhouse et al., 1972). Among the large occupational exposed groups studied approximately 5-10% of the deaths have been due to mesothelioma (Hammond and Selikoff, 1973; Selikoff, 1976; and Selikoff & Seidman, 1991). In Scotland only 5% of the mesotheliomas gave no history of asbestos exposure, while in Canada this lack of association was higher and the Canadian survey gave the annual incidence of about one per million (Gilson, 1973). Other studies have shown the ranges higher up to 23% (Lieben & Pistawka, 1967). Another estimate has projected that as many as 11% of all asbestos workers' deaths in England will be from mesotheliomas (Newhouse and Berry, 1976). Relative risks (RR) ranged between 2.3 -7.0 with a mean of 4.6 for studies published between 1965 & 1975 (Elmes et al., 1965; Newhouse & Thompson, 1965; McEwen et al., 1970; McDonald et al., 1970; Rubino et al., 1972; Ashcroft, 1973; Hain et al., 1974; Zielhuis et al., 1975; & McDonald & McDonald, 1996). Mesotheliomas association with asbestos exposure has generally been very high, generally over 80% and in those that have not stated such exposures when followed up have shown such exposures (Pinto et al, 1995). Dodson et al. (2000) have shown that 10 to 15% of the mesotheliomas arise in the peritoneal area and that fibers also reach the mesentery and omentum in the peritoneal region (Williams et al., 2001).

In a 1960 report of abdominal cancers, 8 cases of peritoneal cancers were reported in women, 4 of which were suggested to be primary from the ovary and 4 only of the peritoneum and all of the cases were diagnosed with asbestosis. One case was reported in the same series in a male ventilator cleaner with asbestosis (Keal, 1960). Previously a case of peritoneal cancer had been reported in a 53 year old asbestos worker with asbestosis and asbestos fibers were found in the tumor tissue (Leicher, 1954). Three cases of peritoneal mesothelioma were reported among 36 asbestosis cases and another case of peritoneal mesothelioma was reported in an insulation worker (Konig, 1960, Van der shoot, 1958).

In another series of 72 asbestosis cases four peritoneal cancers were reported, 1 in a male and 3 in females, 2 of which were thought to be primary ovarian cancers (Bonser et al., 1955). Eleven cases of peritoneal mesothelioma were report among 8 men and 3 women between the ages of 38 to 78, with latency periods of 20 to 46 years and exposures between 10 months and 32 years. The authors reported a "remarkable feature" of the cases was the minimal degree of fibrosis in the lungs (Enticknap & Smither, 1964). Peritoneal mesotheliomas continued to be reported among various occupations with exposure to asbestos including: in a 47 year old insulator & a 46 year old insulator (Heard & Rogers, 1961 & Frenkel & Jager, 1961); 3 cases among radiologically confirmed asbestotics (Thomson, 1962); 4 among asbestos textile workers (Mancuso & Coulter, 1963); 17 cases with known asbestos exposures (Hourihane, 1964); a 60 year old former shipyard insulator [(Owen, 1964); 3 cases among asbestos textile workers (Mann et al., 1966); and 4 cases among asbestos textile workers (O'Donnell et al., 1966). Newhouse & Thompson (1965) reported 27 peritoneal mesotheliomas in London with both occupational as well as some with domestic exposures.

Mesothelioma continues to remain statistically elevated among asbestos workers as demonstrated in the Finish country-wide screening program of 23,285 men and 930 women between 1990 and 1992 (Standard Incidence Ratio (SIR) 2.77; 95% CI 1.66-4.31) (Koskinen et al., 2003). Mortality data have generally underestimated the mortality from mesothelioma on death certificates as there has not been a specific International Classification of Diseases (ICD) code to allow adequate coding for mortality analysis, but hopefully the new 10th revision of the ICD should address this issue. The new ICD-10 codes for mesothelioma are C45.0 for pleural and C45.1 for peritoneal (ICD-10, 1994). Since it has been generally reported that the incidence of mesothelioma in women is much less associated with asbestos exposure, Steenland et al. (2003) suggest that if take-home asbestos exposure were considered the attributable risks may rise to around 90%.

Other sites of mesothelioma have been reported but not of the same incidence as for the pleural or the peritoneal and their relationship to asbestos exposure needs further analysis. Pericardial mesothelioma has also been reported but it has a very low incidence, as reported in one large autopsy study of less than 0.0022% in and by some estimates is related to about 6% of all mesotheliomas (Kobayashi et al., 2001). Dusting of the pericardium with mixed dusts, including asbestos, was reported in an individual when treated for angina pectoris 15 years earlier (Churg et al., 1978). Also, congenital malignant peritoneal mesothelioma has been observed albeit very rarely, with only three cases documented and their association with asbestos is unclear (Paterson et al., 2002).

Fiber Types of Commercial Usage

Amphiboles

Anthophyllite is a member of the amphibole group with a chemical composition of $(Mg, Fe^{+2})_7 Si_8O_{22}(OH,F)_2$ and was principally produce in Finland up 1974 where it was widely used (Liddell & Miller, 1991 & Campbell et al., 1977). Mesothelioma had not been recognized from exposure to anthophyllite until much later than in the three major commercial fiber types (amosite, chrysotile & Crocidolite). It is now clear that mesotheliomas occur among anthophyllite asbestos exposed workers (Tuomi et al., 1989; Tumo, 1992; Tammilehto et al., 1992; Karjalainen et al., 1994). In one study 4 mesotheliomas were observed when the authors expected 0.1 (SIR = 40; 95% CI: 10.90-102.42, as calculated by RAL) (Meurman et al., 1994).

Amosite is a member of the amphibole group with a chemical composition $(Mg,Fe^{+2})_7 Si_8O_{22}(OH)_2$ [Cummingtonite-grunerite]. It was mainly used in asbestos-cement sheet; thermal insulation & roofing products and commonly referred to as brown asbestos (Campbell et al., 1977; Liddell & Miller, 1991; Selikoff & Lee, 1978).

Crocidolite is of the riebeckite mineral of the amphibole group with a chemical formula of $Na_2Fe_3{}^{+2} Fe_2{}^{+3} Si_8O_{22} (OH,F)_2$. It is often referred to as blue asbestos and is more brittle with harsher texture which explains why it is not used in a lot of commercial products such as friction products due to its ability to score the drums of the brake (Campbell et al., 1977; Selikoff & Lee, 1978 & Sheehy et al., 1989).

Tremolite is of the tremolite-actinolite mineral and is found in the amphibole group, even though it is often referred to only as tremolite it has a chemical formula of $Ca_2(Mg, Fe^{+2})_5 Si_8O_{22} (OH,F)_2$. Tremolite is often found as a contaminate of chrysotile asbestos or talc (Campbell et al., 1977; Liddell & Miller, 1998: Selikoff & Lee, 1978 & Sheehy et al., 1989). It has been suggested that milling will remove the tremolite for the chrysotile; however, this is not universally accepted (Roggli et al., 2002).

Tremolite, Mesothelioma & Lung Cancer: Persons using a pure form of tremolite to mix a whitewash, in New Caledonia, called "po" have shown a risk of pleural mesothelioma which is strongly associated with its use (Luce et al., 2000). Other studies have shown similar associations with tremolite containing whitewashes in Cyprus, Greece, Turkey, and in Corsica where environmental exposures to tremolite deposits occur (Yazicioglu et al., 1980; Baris et al., 1998; Baris et al., 1988; Langer et al., 1987; & Rey et al., 1993). Associations with lung cancer have been

much fewer and seem to be complicated with potential confounding factors e.g. alcohol, diet, occupational exposures & smoking. Yarocioglu et al. (1994) reports excesses of lung cancer in areas where the tremolite containing "po" is used.

Serpentines

Chrysotile is the asbestiform variety most commonly used commercially accounting for some 95%+ of the asbestos ever used and is found in the serpentine mineral group with a chemical formula of $Mg_6Si_4O_{10}(OH)_8$. The non-fibrous forms of this serpentine mineral are lizardite and antigorite. As compared to the amphiboles the chrysotile fiber are generally finer with high flexibility and good heat resistance and is commonly referred to as white asbestos (Campbell et al., 1977; Liddell & Miller, 1991& Selikoff & Lee, 1978). The issue of chrysotile-tremolite contamination has been a matter of debate. Some deposits of chrysotile contain trace amounts of tremolite. Canadian chrysotile is said to be contaminated with fibrous tremolite (Liddell et al., 1998) and considered to be less than 1% (Tossavalinen et al., 2001) and with none at all (Frank et al., 1998). The World's largest deposits of chrysotile asbestos are found in Russia at the Bazhenovsk deposit in the town of Asbest close to Ekaterinburg City and accounts for 20% of the world production (Tossavainen et al., 2000). This mining area has been mined since 1889 and samples take and analyzed by PCOM and SEM found only chrysotile and no amphibole minerals were detected, however lung tissue analysis did find tremolite (Tossavainen et al., 1996). In an analysis of lung tissue of 6 Chinese chrysotile miners, all of the bulk samples contained amphibole asbestos (measuring about 0.002 to 0.310% lung tissue) with tremolite fibers found in every sample. While few studies have examined impurities of Chinese chrysotile, with the exception of qualitative analyses of the Qilian mine which showed "little amount" of amphibole and the Chaoyang mine, Liaoning province which also found a small amount of tremolite (Tossavainen et al., 2001). Zimbabwe is also a major producer of chrysotile asbestos has not found tremolite in samples taken for an epidemiology study (Cullen & Baloyi, 1991; Baloyi, 1989). In samples taken from another major deposit of chrysotile in a mine and mill in Balangero, Italy, no tremolite was detected in any of the samples of chrysotile (Piolatto, 1990).

The carcinogenicity of chrysotile asbestos:

Simson reported fibrosis and golden yellow bodies in the lungs of guninea-pigs similar to those found in humans. The animals were exposed 2 hours per day for 50 days in 1925 to chrysotile (Simson,

1928). The results from animal bioassays present a strong case that there is no safe form of asbestos. Wagner et al. (1979), then with the U.K.'s Medical Research Council (MRC), have shown that a commercial grade, Canadian chrysotile, which is used primarily for paint and plastic tile fillers, can induce mesotheliomas when injected intrapleurally into rats, and induce primary lung neoplasm when the animals are exposed by inhalation. Not only does it appear that chrysotile is as potent as crocidolite and the other amphiboles in inducing mesotheliomas after intrapleural injections (Wagner et al., 1973), but also equally potent in inducing pulmonary neoplasm after inhalation exposure (Wagner et al., 1974). In terms of degree of response related to the quality of dust deposited and retained in the lungs of rats, chrysotile appears to be much more fibrogenic and carcinogenic than the amphiboles (Wagner et al., 1974).

Epidemiologic evidence combined with the animal data supports the role that all fiber types, including chrysotile, are responsible in the etiology of lung cancer and mesothelioma as well as other cancers. While most of these studies are of cohorts of workers who were exposed to chrysotile that may have been contaminated with low levels of tremolite, an amphibole form of asbestos, several studies revealed a substantially increased risk of contracting mesothelioma from exposure to chrysotile that did not contain any tremolite contamination. In the first study, Piolatto and his associates examined a cohort of 1094 chrysotile production workers employed at the mine and mill in Balangero, Italy, a site where no tremolite was detected in any of the samples of chrysotile (Piolatto, 1990). Among the 427 deaths, the authors discovered two mesothelioma cases, one confirmed pathologically and one based on radiographic findings and an examination of pleural fluid. While the authors did not report a standard mortality ratio (SMR), in this cohort, it could however be expected that the SMR would have been greater than 2 given the rate of one mesothelioma in 10,000 deaths.

In a similar study, Cullen and Baloyi examined the records of Zimbabwean miners and millers who had been certified as having an occupational lung disease (Cullen & Baloyi, 1991; Baloyi, 1989). Like the chrysotile ore mined in Balangero, Italy, no tremolite was detected in any of the samples. The authors estimated that 6,647 Zimbabweans were engaged in the mining and milling operations at two mines: Shabani and Goths. Among the chosen cohort of 27 miners with sufficient documentation, the authors discovered one mesothelioma case proven by biopsy, one mesothelioma proven by post mortem and one probable mesothelioma based on radiographic findings. They also reported one case of asbestosis probable terminal mesothelioma vs. lung cancer based on chest x-ray only as having a pleural mass 5 years later. Given the rarity of the disease and the size of the exposed population, and even

though the authors did not report an SMR it is most likely that it would have exceeded an SMR of two given the rarity of the disease in a comparison population of non-exposed individuals.

Rogers and his colleagues examined 221 cases of definite and probably mesothelioma obtained from the Australian Mesothelioma Surveillance Program (Rogers et al., 1991 & Henderson, 2000). Among these cases, Rogers "recorded a substantial number of mesothelioma patients in whom the only detectable type of asbestos was chrysotile (Table 9), with evidence of a dose-response effect as reflected in a trend to an increasing odds ratio (OR) at relatively low fibre concentration of less than 10^6 fibers per gram dry lung tissue ($\log_{10}$ = 5.5-6; OR = 8.67).

A 25-year longitudinal study of workers exposed to amphibole-free chrysotile found two confirmed cases of mesothelioma among the exposed workers (Yano et al., 2001). The relative risk for all cancers, adjusted for smoking and age, was 4.29 (CI 95% 2.17, 8.46).

In addition to the studies of uncontaminated, "pure" chrysotile, there have been several studies of populations who were exposed to chrysotile ore and processed chrysotile products, which contained trace amounts of the amphibole tremolite. In the mining context, Camus, Siemiatycki and Meek compared mortality among women in two chrysotile asbestos mining areas in the province of Quebec with mortality among women in 60 control areas. While focusing on lung cancer mortality, the authors discovered a statistically significant increase in mesotheliomas, as evidenced by an SMR of 7.63 with a confidence interval of 3.06 to 15.73 (Camus et al., 1998).

With regard to processed products composed of principally chrysotile asbestos, Nokso-Kollvisto and Pukkala examined a cohort of 8,391 members of the Finnish Locomotive Drivers' Association during the years 1953 and 1991. They found a statistically significant four-fold risk of mesothelioma (Nokso-Kollvisto & Pukkala, 1994). In another study of railroad workers predominantly exposed to chrysotile asbestos, Dr. Thomas Mancuso arrived at a similar conclusion (Mancuso, 1988). Out of a cohort of 181, there were 156 deaths, 14 of which were identified as mesotheliomas constituting 34 percent of all cancer deaths in the study, the incidence of mesothelioma far exceeding a doubling of the risk.

Also, published is a study of workers employed in an asbestos textile, friction and packing manufacturing facility, which utilized 99% chrysotile asbestos. Among the deaths observed in this study, 17 were the result of mesotheliomas, representing 4.3% of the deaths. It was concluded that the study demonstrated an excess risk of mesothelioma to both the males and females studied (Robinson et al., 1979).

Dement & Brown (1993), in a cohort of chrysotile textile workers, found an overall excess of respiratory cancer with and SMR of 2.25 (95% CI: 1.85-2.71) and an SMR of 2.24 (95% CI: 1.83-2.72) for pleural mesothelioma. The chrysotile fibers came exclusively from Quebec, British Columbia, and Rhodesia. In the manufacturing process the fibers mixed with cotton were sprayed with a light mineral oil, which saturated it to about 4% and by the time it reached the spinning looms the oil had diminished to less than 1%. Some have purported that this study's findings might be a result of the mineral oil treatment, however, the authors found from a case-control analysis that only a slight exposure-response reduction occurred for lung cancer when the mineral oil exposures were adjusted for, thus leading the authors to conclude that the mineral oil exposures were insignificant.

Finally, Sturm, et al. reviewed 843 cases of mesothelioma recorded in the German Federal State of Saxony-Anhalt between 1960 and 1990 (Strum et al., 1994). Sixty-seven cases, representing 14% of the total, were directly attributable to a sole exposure to chrysotile asbestos.

When comparing animal studies to human response, based on the epidemiology studies, Kuempel et al. of NIOSH, concluded that chrysotile toxic doses (TDs) in rats compared to humans. Their analysis found that the rat-based risk estimates for lung cancer compared to humans were reasonably concordant to those for the Canadian miners/millers studies while those compared to textile workers were much higher indicating that humans may be more sensitive, however, fiber size studies were not done, but there is evidence that textile workers may have been exposed to longer fibers than those found in the Canadian cohorts (Kuempel et al., 2001).

The 1984 Report of the Royal Commission on Matters of Health and Safety Arising from the Use of Asbestos in Ontario concludes that "All fibre types can cause all asbestos-related diseases, . . ." (Dupre' et al., 1984). This supports the finding of reported cases of mesothelioma among brake mechanics exposed to chrysotile (Langer et al., 1982; and Haucharek, 1987). Mancuso (1988; 1990) further contends, based upon his analysis of railroad machinists, that commercial chrysotile asbestos has caused mesotheliomas and that the risk is greater than previously asserted. There is further concern that chrysotile is rarely found in its pure form and that most chrysotile deposits are contaminated with the amphibole tremolite, which is agreed by experts to be a toxic form of asbestos (Sebastien et al., 1989). In a review of the evidence, Stayner, Dankovic, and Lemen, of the National Institute for Occupational Safety and Health conclude that "Given the evidence of a significant lung cancer risk, the lack of conclusive evidence for the amphibole hypothesis, and

the fact that workers are generally exposed to a mixture of fibers, we conclude that it is prudent to treat chrysotile with virtually the same level of concern as the amphibole forms of asbestos" (Stayner, Dankovic, and Lemen, 1996). Further discussions on the causal connection between chrysotile asbestos and mesothelioma can be found in Lemen (2004).

Two publications highlight the fact that the majority of the world medical community considers chrysotile to be a cause of peritoneal mesothelioma. In 1997, a multi disciplinary gathering of nineteen pathologists, radiologists, occupational and pulmonary physicians, epidemiologists, toxicologists, industrial hygienists, and clinical and laboratory scientists held a meeting in Helsinki, Finland to agree upon criteria for attribution of disorders of the lung and pleura in association with asbestos. Collectively, the group had published over 1000 articles on asbestos and asbestos-associated disorders. The consensus of the group was that *all types* of malignant mesothelioma can be induced by asbestos, with the amphiboles showing greater carcinogenic potency than chrysotile (Tossavainen, A. et al, 1997).

The second publication was a monograph devoted specifically to chrysotile asbestos that was prepared by the International Programme on Chemical Safety in conjunction with the World Health Organization. After an extensive review of the world's literature, this body concluded that *"commercial grades of chrysotile have been associated with an increased risk of pneumonoconiosis, lung cancer and mesothelioma in numerous epidemiological studies of exposed workers."* (IPCS, 1998).

Chrysotile fibers are much more chemically and biologically reactive than amphibole fibers and because of this reactivity with the tissues, they lose their structural elements and divide into smaller fibrils, making their recognition difficult by the usual analytical methods. In fact, many of the fibers are removed from the lung and exhaled back through the bronchi or removed by the lymphatic system to other organs of the body (Marten et al., 1989; Davis, 1979; Davis et al., 1986a; and Davis et al., 1986b). The concentration of dust in the lungs of rats exposed to Canadian chrysotile was only 1.8% - 2.2% of the dust concentration in the lungs of animals exposed to amphiboles (after 24 months of inhalation exposures). Yet the lung tumor incidence and degrees of pulmonary fibrosis were similar in all groups. These findings support the idea that chrysotile fibers cause more cellular injury, fibrosis and lung cancer, than the amphiboles, while at the same time are less readily detected in the tissue after the damage is done. Churg et al. (1989a) concludes that the failure of chrysotile to accumulate in the lung is a result of preferential chrysotile clearance during the first few days to weeks after exposure and that dissolution plays no role in the clearance

and that the preferential clearance may be a result of fragmentation and rapid removal of the chrysotile fibers. This is also supported by Roggli et al. (2002), in that they conclude, as do others, that chrysotile does not accumulate in lung tissue because they are broken down into smaller fibrils that rapidly cleared from the lung. Such chrysotile fibers have been missed by their technique which counted only fibers longer than 5 Um in length. They also conclude that long, thin fibers would likewise be missed, because chrysotile content is poorly detected by the scanning electron microscope (SEM) and thus fiber burden is a poor indicator of total chrysotile exposure and other information must be sought in order to address the question of total body burden of chrysotile. Suzuki et al. (1998) in 92 consecutive cases of mesothelioma observed that the major asbestos type identified in the mesothelial tissues was chrysotile when compared to the chrysotile fiber burden in the lungs of the same cases (79.0% vs. 28.3% respectively). It was found that dogs with mesothelioma, had higher concentrations of chrysotile in their lungs than the control dogs (NRC, 1991).

Malorni et al. (1990) suggests that fiber penetration can rearrange the cytoskeletal apparatus of the cell and that this could indicate an interaction between the chrysotile fibers and the normal mitotic process, since giant multinucleated cells are formed. Churg et al. (1989b) further believes that the short fibers may be more fibrogenic than previous animal data suggest and deserves further study.

Biologic plausibility seeks to determine if the theory of causation fits known mechanisms of injury causation. While it is impossible to have a complete understanding of the mechanisms of cancer causation, the biologic facts known about the various asbestos fibers and how they cause disease are consistent with the postulate that chrysotile asbestos fibers are capable of producing mesotheliomas. First, it has been long known that it is not the chemical composition of the various asbestos fibers that is important in their ability to produce disease, the health effects of asbestos are related primarily to their morphology, their shape and size. Many researchers contend that the potency of crocidolite is related to its thin diameter. Similarly, chrysotile fibers have a tendency to cleave longitudinally creating extremely thin fibrils.

Second, it is universally accepted that chrysotile asbestos is carcinogenic and capable of causing or contributing to the development of lung cancer.

Third, mesotheliomas develop in the pleura, peritoneum and other serosal surfaces of the body. It is universally accepted that chrysotile is a cause of cancer in the lung and that it also migrates to the mesothelial linings of the body (Suzuki & Yeun, 1991; Kolyema & Suzui, 1991;

Suzuki et al., 1998; & Sebestain et al., 1980). Sebastien et al. (1979) found that all the fibers in the pleural were chrysotile when there was no predominance in the parenchymal samples, leading the authors to conclude that lung parenchymal retention is not a good indicator of total body burden of asbestos retention. Translocation of asbestos fibers to other organs is also well documented. In addition, a series of 168 cases reviewed by Suzuki and Yuen of mesothelioma confirmed:

> "1. Asbestos fibers were present in almost all of the lung and mesothelial tissues from the mesothelioma cases. 2. The most common types of asbestos fibers in lung were either an admixture of chrysotile with amphiboles, amphibole alone, and occasionally chrysotile alone. In mesothelial tissues, most asbestos fibers were chrysotile. 3. In lung, amosite fibers were greatest in number followed by chrysotile, crocidolite, tremolite/actinolite, and anthophyllite. In mesothelial tissues, chrysotile fibers were 30.3 times more common than amphiboles. 4. In some mesothelioma cases, the only asbestos fibers detected in either lung or mesothelial tissue were chrysotile fibers. 5. The average number of asbestos fibers in both lung and mesothelial tissues was two orders of magnitude greater than the number found in the general population. 6. The majority of asbestos fibers in lung and mesothelial tissues were shorter than 5 μm in length." (Suzuki & Yuen, 2002).

Since chrysotile is carcinogenic and is present in high concentrations in the mesothelial linings where the mesothelioma is induced, it is biologically plausible that it causes or contributes to the cause of mesothelioma. This is also shown by many mechanistic and molecular studies that indicate how chrysotile may cause mesothelioma. Fiber penetration can rearrange the cytoskeletal apparatus of the cell and this could indicate an interaction between the chrysotile fibers and the normal mitotic process, since giant multinucleated cells are formed. These studies indicate that chrysotile penetrates the cell, enters the nucleus and induces abnormal chromosome formations in dividing cells (Malorni et al., 1990). Some of these abnormalities include the deletion of the P53 gene growth (Leversse, 1997). Inhaled chrysotile asbestos induced, at the fiber deposition sites, the expression of p53 protein (Mishre et al., 1997), which suggests that the p53 protein can accumulate in the lung tissue after chrysotile exposure. Additionally a study of the phosphorylation of the p53 protein in A549 human pulmonary epithelioal cells, exposed to asbestos, it was found that chrysotile asbestos, on a per-weight basis was more potent in inducing Ser15 phosphorylation and accumulation of the p53 protein than was crocidolite (Matsuoka et al., 2003). Another recent study has indicated

particle stimulation chemiluminescence (CL) production by polymorphonuclear leuocytes has been used to evaluate the pathogenicity of mineral fibers understanding that reactive oxygen metabolites as measured by CL is etiopathogenically related to fiber toxicity. These findings may indicate that neither the total number nor the specific range of fiber dimensions are solely determinate of the CL production and thus other physiochemical factors like surface reactive characteristics of the milled fibers may play a role in the etiology of disease (Iwata & Yano, 2003). Pott (1993) has questioned fiber dimension as a reliable yardstick for the carcinogenic dose and that inhalation studies of rats, as a surrogate for human inhalation effects, are misleading in that rats are known obligatory nose breathers. These findings bring into question the Stanton el al. hypothesis on fiber diameter and length being the only determinates of the carcinogenicity of fibers (Stanton et al., 1997). Pott (1993) also addresses the use of intrapleural and intraperitoneal route in examining the carcinogenic potential of inorganic fibers, which has been criticized emphatically. Pott concludes that the consistency of such an argument is not supported when, for example, the inhalation studies with crocidolite that doesn't result in either lung tumors or mesothelioma, even though the fiber concentrations in the lung are very high.

These epidemiological findings along with the results of the experimental studies leave no doubt that the scientific evidence supports the carcinogenicity of chrysotile alone in the induction of mesothelioma.

Asbestos Exposure Guidelines,

The current standards for the "supposedly" safe use of asbestos have all been shown to be not effective. Except for bans, the lowest occupational exposure standard do not proved adequate protection from exposure to asbestos. The United States standard for asbestos is currently 0.1 fibers/cc over an 8 hour time weighted average, which equates to the inhalation of 1,200,000 fibers per day. The exposure-response relationship for lung cancer is linear (Peto, 1989). At this current standard the risk of death is 3.4 per 1,000 at 0.1 fibers/cc (OSHA, 1986). Even at this new limit it can be clearly seen that the risk for dying from cancer is not zero nor does it even approach it. Dement & Brown (1993) reported statistically significant excess for lung cancer at exposures as low as less than 3 fiber/years. Case reports exist, also some epidemiology evidence, of short exposures on the order of a few days to months give rise to asbestos related cancers (Seidman et al., 1979). The WHO (1989) stated that *"[T]he human evidence has not demonstrated that there is a threshold exposure level for lung cancer or mesothelioma, below which exposure to asbestos dust would not be free of hazard to health".*